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Original Article

Behaviorally meaningful functional networks mediate the effect of Alzheimer's pathology on cognition

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Tau pathology is associated with cognitive impairment in both aging and Alzheimer's disease, but the functional and structural bases of this relationship remain unclear. We hypothesized that the integrity of behaviorally meaningful functional networks would help explain the relationship between tau and cognitive performance. Using resting state fMRI, we identified unique networks related to episodic memory and executive function cognitive domains. The episodic memory network was particularly related to tau pathology measured with positron emission tomography in the entorhinal and temporal cortices. Further, episodic memory network strength mediated the relationship between tau pathology and cognitive performance above and beyond neurodegeneration. We replicated the association between these networks and tau pathology in a separate cohort of older adults, including both cognitively unimpaired and mildly impaired individuals. Together, these results suggest that behaviorally meaningful functional brain networks represent a functional mechanism linking tau pathology and cognition.

Key words: network; fMRI; cognition; aging; Alzheimer's.

Introduction

The microtubule-associated protein tau is primarily involved in stabilizing the neural cytoskeleton (Dehmelt and Halpain 2004), but when hyperphosphorylated, it becomes pathological and dissociates to form neurofibrillary tangles both intra- and extracellularly (Hanger et al. 2014). Along with diffuse fibrillar amyloid-beta (Aβ), the stereotyped spread of tau from the medial temporal lobe to areas across the cortex is one of the hallmark neuropathologies of Alzheimer's disease (AD) (Braak and Braak 1991). Tau pathology is also known to be present in aging, with accumulation in the medial temporal lobe observed in almost all older adults, even without cognitive impairment (Crary et al. 2014). In contrast to the weak relationship found between Aβ and cognitive performance, tau pathology burden is closely associated with cognitive performance both cross-sectionally and over time (Schöll et al. 2016; Aschenbrenner et al. 2018; Maass et al. 2018; Sperling et al. 2019) in older adults. Episodic memory is one of the cognitive domains that declines earliest in the presence of AD pathology, even in cognitively unimpaired (CU) older adults (Maass et al. 2018; Sperling et al. 2019; Ziontz et al. 2019), but executive function may also be impaired shortly after, particularly for individuals with mild cognitive impairment (MCI) and AD (Buckner 2004; Bejanin et al. 2017; Hanseeuw et al. 2019; Ossenkoppele et al. 2022; Tideman et al. 2022). Still, despite the preponderance of evidence linking tau to cognitive performance in aging and AD, the mechanisms by which tau deposition results in cognitive decline are not well understood.

Most explanations of the link between tau pathology and cognition have focused on the role of neurodegeneration. Tau pathology is associated with lower regional brain volume and cortical thickness (Mak et al. 2018; Berron et al. 2021; Harrison et al. 2021), and the baseline spatial pattern of tau accumulation predicts future atrophy rates beyond the effects of baseline Aβ or cortical thickness (La Joie et al. 2020). Indeed, tau may lead to neural death and regional atrophy via disruption of cytoskeletal integrity in brain regions where it accumulates (Spillantini and Goedert 2013; Mak et al. 2018), and the presence of tangles in affected regions may further disrupt cell signaling and maintenance (Harris et al. 2020). Still, studies examining neurodegeneration as a potential mechanism have shown that much of the association between tau and cognition is unexplained by structural measures, particularly for individuals in the earliest stages of decline. A mediating effect of gray matter volume (Bejanin et al. 2017) and cortical thickness (Ossenkoppele et al. 2021) has been observed in individuals diagnosed with AD, though CU individuals often do not show a definitive mediating role for brain structure in the relationship between tau pathology and cognition (Berron et al. 2021; Ossenkoppele et al. 2021). In each of these studies, a great

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degree of variance in the relationship between tau pathology and cognition remains after accounting for brain structure. It may be that factors related to brain function, rather than structure, play a particularly important role in the relationship between tau pathology and cognition at the earliest stages of disease.

Inter-correlation of the spontaneous blood oxygen level-dependent (BOLD) signal, reflecting neural activity and measured with functional magnetic resonance imaging (fMRI), has been used for decades to define functionally correlated regions of the brain. This phenomenon is described as intrinsic connectivity as regional patterns of coherence arise in the absence of external stimulus, with topography at rest robust across individuals and closely matching functional connections observed during task performance (Fox et al. 2005; Fox and Raichle 2007). Networks reflecting these patterns of functional connectivity (FC) can be observed during many different cognitive tasks or in the absence of a specific paradigm (Cole et al. 2014), and functional architecture at rest may in fact shape networks observed during task performance (Cole et al. 2016). Interestingly, atrophy patterns of different neurodegenerative syndromes topographically resemble distinct intrinsic connectivity networks in healthy individuals (Seeley et al. 2009). Furthermore, patterns of tau accumulation in different clinical variants of AD mirror (Ossenkoppele et al. 2016) and can be predicted by patterns of connectivity in distinct brain networks (Therriault et al. 2022). Some of these networks, such as the default mode and salience networks, show alterations in the strength of connectivity that are related to Aβ and tau pathologies (Schultz et al. 2017) and decline in cognitive function over time (Buckley et al. 2017). Given the close relationship between intrinsic FC and patterns of tau accumulation, network connectivity may be a critical factor in the relationship between tau pathology and cognitive performance.

Functional networks can be identified using a wide array of approaches, with one of the most well-known parcellations organizing the brain into 7 distinct, stable networks that span the entire cerebral cortex (Yeo et al. 2011). Alternatively, networks of functional connections can be identified in terms of their relationship to specific cognitive performance. One influential study (Rosenberg et al. 2015) defined a whole-brain network of functional connections most closely related to performance on a sustained attention task and found that the overall strength of this network during the task predicted attentional performance in an independent cohort, both during a different attention task and at rest. Similar methods have been used to identify brain networks reflecting varied outcomes, such as pain (Lee et al. 2021) and creative ability (Beaty et al. 2018), as well as performance in cognitive domains including executive function (Henneghan et al. 2020), short-term memory (Ju et al. 2023), fluid intelligence (Greene et al. 2018; Gao et al. 2019), attention (Fountain-Zaragoza et al. 2019), and processing speed (Gao et al. 2020). Still, though considerable evidence indicates that intrinsic brain networks are robust and generalizable, few studies to date have leveraged these kinds of functional networks to understand the impact of pathology on cognitive function. Further, this type of approach relies on selecting a priori thresholds for identifying connections and often results in networks of hundreds or thousands of components that make it difficult to explore biologically meaningful pathways and regional interactions. Approaches that result in much sparser networks have a particular advantage in the study of aging and AD, as evidenced by a recent study identifying highly sparse functional networks predicting cognitive reserve in older adults (Boyle et al. 2023). Sparse networks can be viewed as more biologically and cognitively relevant in that it is easier to examine those connections that are involved in cognitive performance and simplifies the analysis of which connections may be impacted by pathology and/or atrophy in regions known to be affected by neurodegenerative disease. In this way, network sparsity allows for the examination of the relevance of specific connections and regions involved in both cognitive function and neurodegenerative disease.

In this study, we investigated the role of behaviorally meaningful functional brain networks in mediating the relationship between tau pathology accumulation and cognitive performance. We used a data-driven network definition procedure to identify networks of resting-state functional connections in older adults that are closely related to performance on neuropsychological tests in 2 distinct cognitive domains: episodic memory and executive function. We hypothesized that this approach, allowing for network identification without introducing a priori thresholds for selecting connections, would nonetheless yield networks with a much sparser and more interpretable subset of connections than conventional approaches (Rosenberg et al. 2015; Shen et al. 2017). We further hypothesized that the overall strength of these networks would be related to tau pathology accumulation and would play a mediating role in the relationship between tau and cognitive function, particularly in the episodic memory domain. Finally, to assess the robustness of this approach, we replicated our findings in an independent dataset, demonstrating that behaviorally defined networks represent a functional mechanism for the relationship between pathology and cognitive performance.

Materials and methods

Participants

Berkeley cohort

We included data from 120 CU older adults from the Berkeley Aging Cohort Study (BACS). Demographic information for all BACS participants is shown in Table 1. All participants underwent 3T structural MRI, resting state 3T functional MRI, and a standard neuropsychological assessment. We excluded 2 participants on the basis of excessive head motion during the rsfMRI scan, defined as >20% of all volumes being flagged as outliers during artifact detection. Of the remaining sample, 103 individuals underwent tau PET imaging using ^{18}F-Flortaucipir (FTP), and we excluded an additional 9 participants whose resting state fMRI data was collected more than 1 yr from the closest corresponding tau PET scan (M = 125.6, SD = 138.4 d). Additional inclusion criteria for this study were 60+ yr of age, cognitively normal status (Mini Mental State Examination score ≥ 25 and normal neuropsychological examination, defined as within 1.5 SDs of age, education, and sex adjusted norms), no serious neurological, psychiatric, or medical illness, no major contraindications found on MRI or PET, and independent community living status. This study was approved by the Institutional Review Boards of the University of California, Berkeley, and the Lawrence Berkeley National Laboratory (LBNL). All participants provided written informed consent.

ADNI cohort

We included data from 140 older adults aged 60–100 yr old from the AD Neuroimaging Initiative 3 (ADNI3) who had all undergone 3T structural MRI and resting state 3T functional MRI and tau PET imaging using ^{18}F-FTP. Demographic information for all ADNI participants is shown in Table 1. We excluded 8 participants due to errors in warping rsfMRI data to MNI space and excluded an additional 13 participants due to excessive head motion, again

Table 1. Demographics for participants with resting state functional magnetic resonance imaging data (rsfMRI) from the Berkeley aging cohort study (BACS) and Alzheimer's Disease Neuroimaging Initiative (ADNI) samples.

BACS rsfMRI		ADNI3 rsfMRI		
Mean (SD) or n (%)	**CU ($n = 118$)**	**CU ($n = 75$)**	**MCI ($n = 44$)**	**BACS vs. ADNI**
Age	78.2 (6.5)	70.9 (8.1)	72.6 (7.1)	$P < 0.001$
MMSE	28.7 (1.2)	28.9 (1.6)	27.5 (2.6)	$P = 0.15$
Education (yrs)	16.9 (2.0)	16.5 (2.4)	16.3 (2.6)	$P = 0.07$
Sex (female)	68 (58%)	52 (69%)	14 (32%)	$P = 0.84$

CU, cognitively unimpaired; *MCI*, mild cognitive impairment; *MMSE*, mini mental state examination.

defined as >20% of all volumes being flagged as outliers. Individuals aged 60+ yr from ADNI3 were included based on the availability of high temporal resolution rsfMRI (TR = 0.607) within 1 yr of a corresponding FTP PET scan ($M = 29.4$, SD = 94.5 d).

MRI acquisition and processing

In BACS, structural and functional MRI data were acquired on a 3T TIM/Trio scanner (Siemens Medical System, software version B17A) using a 32-channel head coil. A T1-weighted whole brain magnetization prepared rapid gradient echo (MPRAGE) image was acquired for each subject (voxel size = 1 mm isotropic, TR = 2300 ms, TE = 2.98 ms, matrix = 256 × 240 × 160, FOV = 256 × 240 × 160 mm^3, sagittal plane, 160 slices, 5 min acquisition time). Resting state functional MRI was then acquired using T2∗-weighted echo planar imaging (EPI, voxel size = 2.6 mm isotropic, TR = 1.067 s, TE = 31.2 ms, FA = 45, matrix 80 × 80, FOV = 210 mm, sagittal plane, 300 volumes, anterior to posterior phase encoding, ascending acquisition, 5 min acquisition time). During resting state acquisition, participants were told to remain awake with their eyes open and focused on a white asterisk displayed on a black background.

In ADNI3, structural and functional MRI data were acquired on 3T scanners with a standardized protocol across all sites. A T1-weighted whole brain MPRAGE image was acquired for each subject (voxel size = 1 mm isotropic, TR = 2300 ms, TE = min full echo, matrix = 208 × 240 × 256, FOV = 208 × 240 × 256 mm^3, sagittal plane, 256 slices, 6 min acquisition time). Resting state functional MRI was then acquired using EPI-BOLD (voxel size = 2.5 mm isotropic, TR = 0.607 s, TE = 30 ms, FA = 53, matrix 220 × 220, FOV = 160 mm, sagittal plane, 976 volumes, anterior to posterior phase encoding, ascending acquisition, 10 min acquisition time, further details at https://adni.loni.usc.edu/wp-content/uploads/2017/07/ADNI3-MRI-protocols.pdf).

Structural T1-weighted images were processed using statistical parametric mapping (SPM12). Images were first segmented into gray matter, white matter, and CSF components in native space. DARTEL-imported tissue segments for all individuals in the sample were used to create a study-specific template, which was then used to warp native space T1 images and tissue segments to MNI space at 2 mm isotropic resolution. Finally, native space T1 images were segmented with Freesurfer v.5.3.0 using the Desikan–Killany atlas parcellation (Desikan et al. 2006). Separate DARTEL study-specific templates were created for BACS and ADNI, such that functional and structural images were warped to MNI space using a template defined separately in each cohort.

Resting-state fMRI images from BACS and ADNI3 were preprocessed using a nearly identical SPM12 pipeline, with slight differences to account for different acquisition parameters. Slice time correction was applied in BACS to adjust for differences in acquisition time for each brain volume, but this was not done in ADNI because of the low TR resting state data. In both cohorts, all EPIs were realigned to the first acquired EPI, and translation and rotation realignment parameters were output. Each EPI was next coregistered to each individual's native space T1 image. Next, all resting state EPIs and structural images were warped to a cohort-specific DARTEL template in 2 mm isotropic MNI space from structural preprocessing. These smoothed rsfMRI images in MNI space were used to extract the time series of each ROI in seed-to-seed FC analyses. To further adjust for confounds of head motion, mean framewise displacement was computed for each rsfMRI scan and included as a covariate in all subsequent analyses. Across all subjects, after excluding participants with excessive head motion, mean framewise displacement was 0.18 mm (SD: 0.06) in BACS, and 0.19 mm (SD: 0.07) in ADNI.

FC analyses

ROI-to-ROI FC was assessed using the CONN FC toolbox (version 17e) (Whitfield-Gabrieli and Nieto-Castanon 2012) implemented in MATLAB version 2019b (The Mathworks Inc., Natick, MA, USA). ART motion detection was first performed to identify volumes of high motion, using a movement threshold of >0.5 mm/TR and a global intensity z-score of 3. Outlier volumes were flagged and included as spike regressors during denoising. Denoising was performed with translation and rotation realignment parameters and their first-order derivatives, as well as anatomical CompCor (the first 5 components of the time series signal from white matter and CSF). A band-pass filter of 0.008–0.1 Hz and linear detrending were applied to the residual time series. For each individual, denoised time series were extracted for 246 ROIS from the Brainnetome Atlas (Fan et al. 2016). Each of these time series was then correlated (Pearson's r) and transformed (Fisher r to z), resulting in a 246 × 246 connectivity matrix.

Network definition procedure

Behaviorally meaningful functional networks were defined in a similar fashion to previous network-building approaches (Shen et al. 2017), taking a FC matrix and behavioral outcome measure for each individual as inputs and generating a network across the sample consisting of a subset of all possible connections in the brain. Each connection (30,135 unique ROI-ROI pairs in the 246 × 246 matrix) was treated as a regressor in a regularized linear model with behavioral performance as the outcome. A least absolute shrinkage and selection operator (LASSO) (Tibshirani 1996) penalty (λ) was applied to the beta weights of each regressor, such that only a sparse subset of regressors survived the penalty to remain nonzero. An appropriate λ penalty was selected by computing the Bayesian information criterion (BIC) (Schwarz 1978) for

each model using the equation:

$$\mathrm{LL} = -\frac{n}{2}\left(1 + \ln\left(\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2\right)\right)$$

where LL is the log likelihood of the model, n is the sample size, y is the observed data, and $\hat{y}$ is the outcome predicted by each model with a given λ, and the using the equation:

$$\mathrm{BIC} = -2\mathrm{LL} + a \ln n$$

where a is the number of nonzero features included in the model. BIC was computed for models iterating through 1,000 λ hyperparameter values, and the model with the lowest BIC (i.e. best explanatory power adjusting for the number of regressors) was selected. This data-driven LASSO+BIC procedure does not require the selection of an arbitrary significance threshold and only keeps regressors with very high beta values, meaning those that are the most relevant to the behavioral outcome measure. The resulting networks tend to exclude spurious or collinear relationships between behavior and connectivity, making them highly sparse and more interpretable. Overall network strength was then computed for each individual by summing the connectivity values (Fisher z-transformed correlations) for every ROI-ROI connection in the network (Shen et al. 2017).

PET acquisition and processing

In BACS, PET was acquired for all participants at LBNL. Tau burden was assessed with ^{18}F-FTP synthesized at the Biomedical Isotope Facility at LBNL, as previously described (Schöll et al. 2016). Data were collected on a Biograph TruePoint 6 scanner (Siemens, Inc.) 75–115 min post-injection in listmode. Data were then binned into 4 × 5 min frames from 80–100 min post-injection. CT scans were performed before the start of each emission acquisition. In ADNI, PET data were collected using a standardized protocol of 6 5-min time windows 75 to 105 min after injection. All PET images were reconstructed using an ordered subset expectation maximization algorithm with attenuation correction, scatter correction, and smoothing with an 8 mm Gaussian kernel.

Processing of FTP images was carried out in SPM12 and Freesurfer. Images were realigned, averaged, and coregistered to 3T structural MRIs. Standardized uptake value ratio (SUVR) images were calculated by averaging mean tracer uptake over the 80–100 min data and normalized with an inferior cerebellar gray reference region. The mean SUVR of each ROI (structural MRI FreeSurfer segmentation) was extracted from the native space images. SUVR images were then warped to 2 mm of MNI space for voxelwise analyses using the cohort-specific DARTEL template produced from structural data (see above). No additional spatial smoothing was applied.

Neuropsychological measures

Episodic memory and executive function cognitive domain performance were measured using neuropsychological assessment data collected closest in time to each individual's rsfMRI scan (M = 129.5, SD = 73.2 d). Composite measures were computed by averaging the z-transformed individual test scores using the mean and SD of the sample (Maass et al. 2018). The episodic memory domain composite included scores from the California Verbal Learning Test (CVLT) immediate free recall, CVLT long-delay free recall, Visual Reproduction I (immediate recall), and Visual Reproduction II (delayed recall) tasks. The executive function domain composite included scores from the Trails A, Trails B, Stroop Correct in 60 s, and Digit Symbol Substitution tasks. In the ADNI sample, episodic memory (adni_mem) and executive function (adni_ef2) cognitive domain scores were downloaded from the publicly available computed online repository using methods described previously (https://ida.loni.usc.edu/download/files/study/ce0a4966-84bf-4a17-bacc-99e98277e325/file/adni/ADNI_Methods_UWNPSYCHSUM_March_2020.pdf).

Statistical analyses

Following FC analyses, network definition was carried out in Python using a combination of internal code and the *pycasso* package (https://pypi.org/project/pycasso/). All subsequent statistical analyses were carried out in R version 4.2.0. Linear regression models in the {stats} package were used to assess the relationship between network strength and tau pathology, adjusting for age, sex, mean framewise displacement, the interval between rsfMRI and tau PET acquisition, and the interval between rsfMRI and cognitive testing. All analyses involving neuropsychological measures were additionally adjusted for years of education. The {lavaan} package was used to carry out multiple mediation analyses, with 1,000 bootstrapped iterations used to determine statistical significance. The percent mediated by each factor was computed by dividing the indirect effect of each factor by the total effect of the relationship.

Data visualization

Networks were rendered and visualized using the BioImage Suite Connectivity Viewer, part of the BioImage Suite Web 1.2.0 browser tool (https://bioimagesuiteweb.github.io/webapp/index.html). Voxelwise analysis results were visualized using the *nilearn* glass-brain plotting function in Python (https://nilearn.github.io/dev/modules/generated/nilearn.plotting.plot_glass_brain.html). Scatter plots were created using the {ggplot2} package in R to visualize effects from linear regression models.

Results

Network identification captures cognition-specific connections across the brain

Resting state fMRI data from 118 CU older adults aged 60–94 (M = 78.2 SD = 6.5 yr) from BACS (Table 1) were used to identify distinct episodic memory and executive function networks. We computed resting state FC (rsFC) as the Pearson's correlation coefficient (z-transformed) between all regions of interest (ROIs) in a 246-ROI parcellation (Brainnetome Atlas) (Fan et al. 2016). Using the data-driven network definition procedure (Materials and methods), we selected pairwise connections specific to each behavioral domain by regressing each unique connection against either an episodic memory or executive function composite score measured closest in time to the fMRI scan (M = 129.5, SD = 73.2 d). A LASSO penalty (λ) was applied to identify connections with the greatest positive association to the behavioral domain score, iterating over many possible λ values to select the model with the lowest BIC. The resulting sample network masks were then applied to each individual's connectivity matrix, and rsFC values for each connection in the network were summed to determine subject-specific overall network strength (Fig. 1A).

This approach identified an episodic memory network comprising 63 functional connections, including between brain areas often implicated in memory processing, such as hippocampus, medial parietal, anterior temporal, and prefrontal regions (Fig. 1B). An executive function network comprising 60

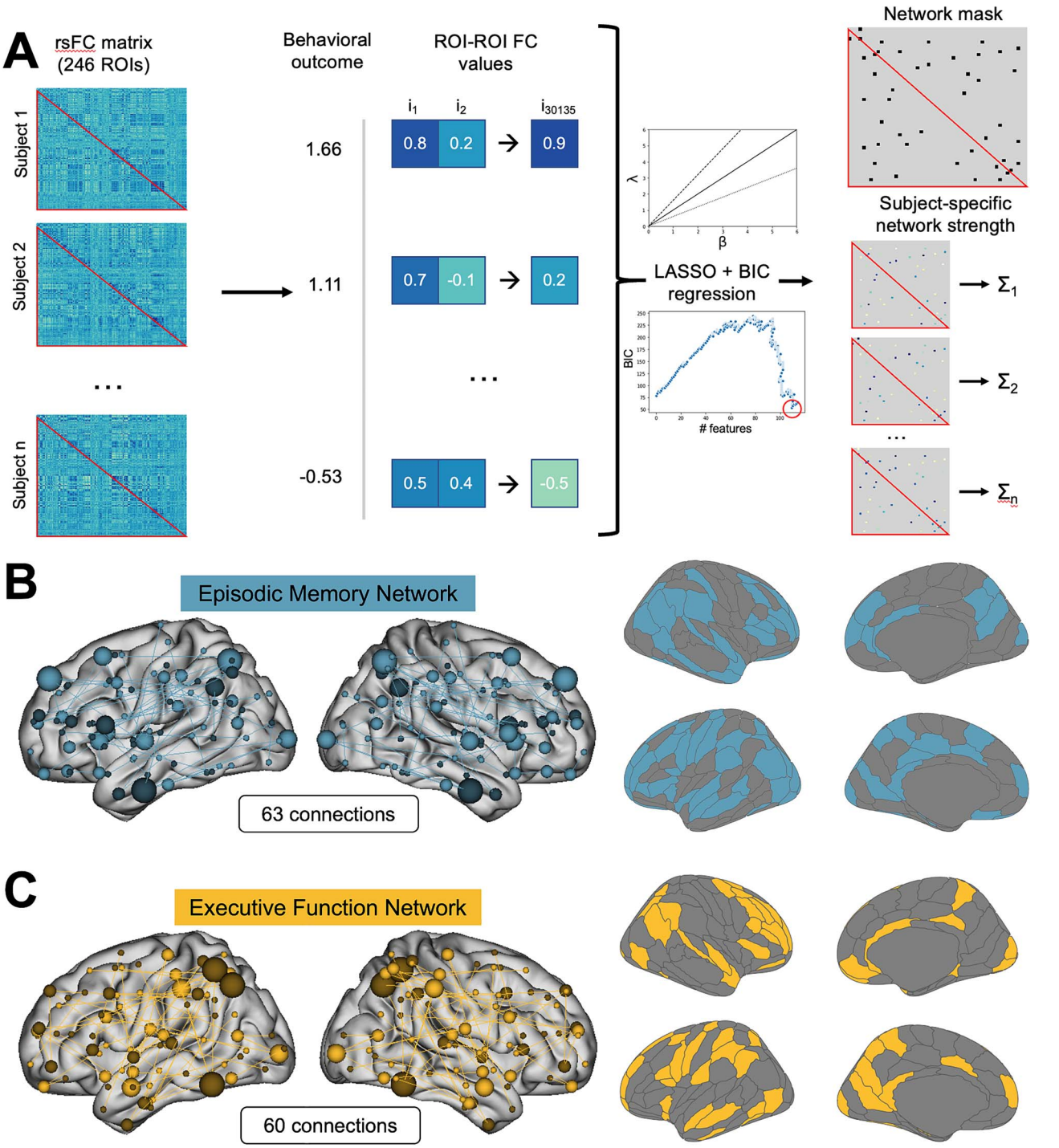

Fig. 1. Behavioral functional networks in cognitively unimpaired older adults. A) In network definition, all unique pairwise rsFC values for each individual were regressed against a behavioral outcome measure. A LASSO penalty (λ) was applied to the β of each positive pairwise connection to select a sparse subset of connections, iterating over 1,000 λ values to identify the model with the lowest Bayesian information criterion (BIC). A network mask can then be projected onto cortical ROIs, and subject-specific network strength is computed by summing rsFC values for each network connection (see methods). B) Episodic memory and C) executive function networks, with spheres centered within connected regions and size corresponding to the number of connections to each region. Darker-colored spheres correspond to nodes in the left hemisphere, and lighter-colored spheres correspond to nodes in the right hemisphere. Cortical surface renderings (right) depict regions connected by each network.

connections between prefrontal, superior parietal, and lateral temporal regions was also identified (Fig. 1C). Networks defined by these 2 cognitive domains were markedly distinct, with only 2 identical ROI-ROI connections and limited spatial overlap of connected regions (Dice Similarity Coefficient = 0.07). After adjusting for age, sex, years of education, mean framewise displacement, and time between rsfMRI and cognitive testing, subject-specific network strength was, as expected, highly correlated with performance in the cognitive domain by which it was defined: episodic memory network strength with episodic memory performance ($r = 0.58$), and executive function network strength with executive function performance ($r = 0.55$). Episodic

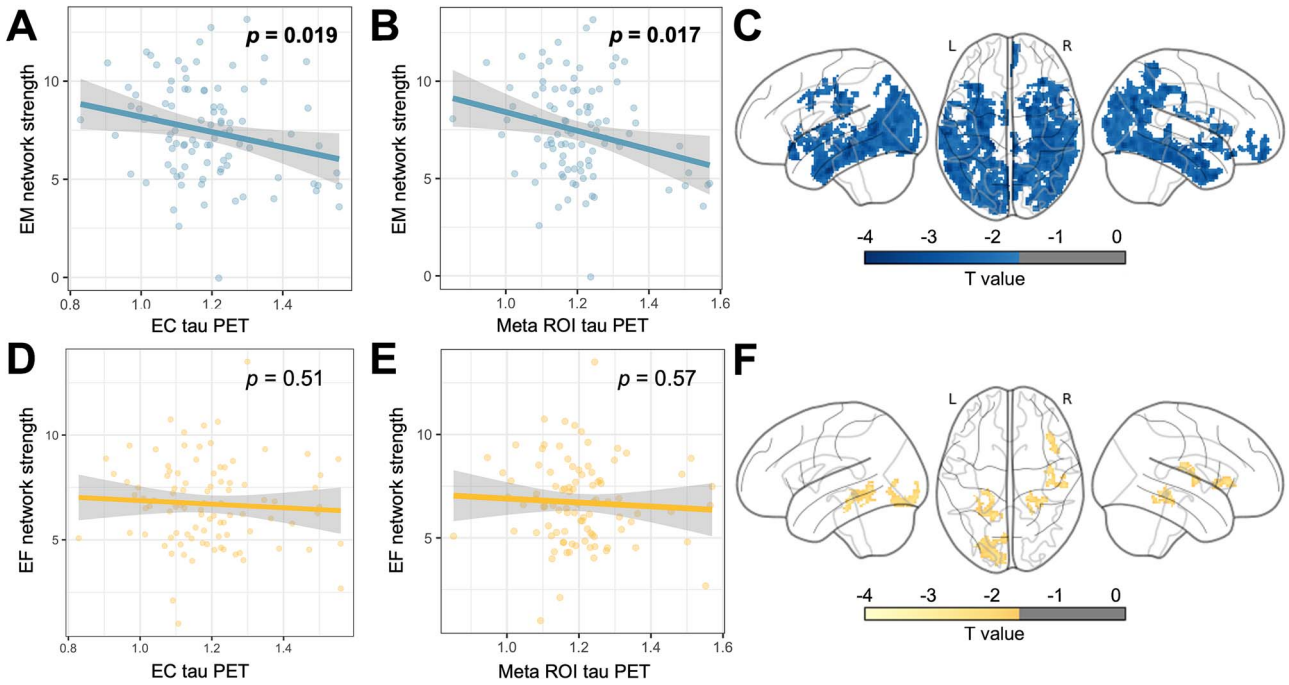

Fig. 2. Tau pathology burden is associated with lower memory network strength. A) Association between episodic memory (EM) network strength and tau PET signal in EC and B) temporal meta ROI adjusting for age and sex. C) Voxelwise association between episodic memory network strength and tau PET signal adjusted for age and sex. D) Association between executive function network strength and tau PET signal in EC and E) temporal meta-ROI adjusting for age and sex. F) Voxelwise association between executive function (EF) network strength and tau PET signal. Voxelwise analyses used an exploratory threshold ($k > 100$, $P < 0.05$ unc) to validate the use of EC and temporal meta-ROI for as relevant regions for associations with network strength.

memory network strength exhibited a weaker correlation with executive function performance ($r = 0.18$), as did executive function network strength with episodic memory performance ($r = 0.18$; Fig. S1).

Tau pathology burden is associated with lower memory network strength

We next aimed to characterize how the strength of these networks was related to age and tau pathology burden. Age was negatively correlated with the overall strength of both episodic memory ($r = -0.24$, $P = 0.010$) and executive function networks ($r = -0.19$, $P = 0.038$; Fig. S2). We then examined the tau PET standard uptake value ratio (SUVR) in the entorhinal cortex (EC) as well as a previously validated AD-signature temporal meta-ROI comprising EC, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal gyri (Jack et al. 2017). We used linear regression models adjusting for age, sex, mean framewise displacement, the interval between rsfMRI and tau PET, and the interval between rsfMRI and cognitive testing to test the association between network strength and tau pathology burden. The greater tau PET signal in EC was associated with lower episodic memory network strength ($\beta = -4.11$, $P = 0.019$; Fig. 2A), as was the greater temporal meta-ROI tau signal ($\beta = -4.94$, $P = 0.017$; Fig. 2B). By contrast, neither tau PET burden in EC ($\beta = -0.97$, $P = 0.51$; Fig. 2D) nor the temporal meta ROI ($\beta = -1.00$, $P = 0.57$; Fig. 2E) was associated with executive function network strength.

To verify that EC and the temporal meta-ROI were appropriate regions to test the association between network strength and tau pathology burden and to explore other potential regional relationships, we examined the voxelwise association between tau PET signal and strength of each network separately, adjusting for age and sex. Using an exploratory threshold ($k > 100$, $P < 0.05$), we found an association between tau PET and episodic memory network strength in medial temporal and lateral temporal regions that captures the typical pattern of tau deposition in AD (Leuzy et al. 2021) and which largely overlaps with the temporal meta-ROI (Fig. 2C). A notably sparse pattern of associations was observed between tau PET and executive function network strength (Fig. 2F).

Memory network strength mediates the association between pathology and cognition

Next, we tested whether episodic memory or executive function networks would mediate the relationship between tau pathology and cognitive function, particularly compared to structural measures of neurodegeneration. We used multiple mediation models to assess the extent to which the association between temporal meta ROI tau accumulation and cognitive domain score is mediated by both network strength and cortical thickness in this same meta ROI, including both functional and structural effects in the same model. We found that episodic memory network strength significantly mediated 50.1% of the total effect of EC tau on memory performance ($P = 0.026$), while EC cortical thickness only mediated a nonsignificant ($P = 0.18$, 15.8%) proportion of this relationship (Fig. 3A). Similarly, episodic memory network strength mediated 48.5% of the total effect of meta ROI tau on episodic memory performance ($P = 0.009$), while meta ROI cortical thickness only mediated a nonsignificant (20.8%, $P = 0.13$) proportion of this relationship (Fig. 3B). Using bilateral hippocampal volume as an alternative structural measure did not change this result, as episodic memory network strength mediated 51.5% of the total effect ($P = 0.003$), while hippocampal volume mediated a nonsignificant ($P = 0.25$, 10.9%) proportion of the effect. In contrast, neither executive function network strength ($P = 0.42$) nor

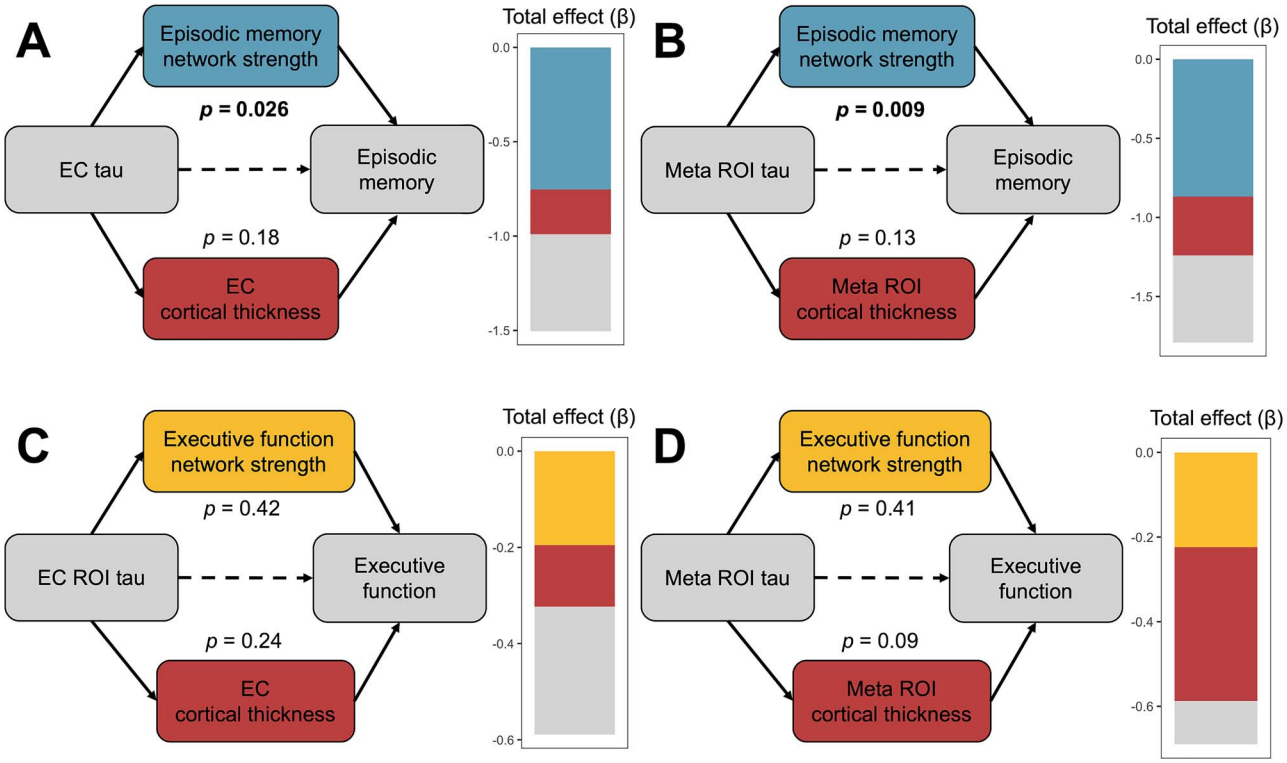

Fig. 3. Episodic memory network strength mediates the association between tau pathology and cognitive performance. Multiple mediation models demonstrate that episodic memory network strength mediates the relationship between tau pathology and cognition to a greater degree than cortical thickness, both A) in EC and B) in the meta ROI. Neither executive function network strength nor cortical thickness mediates the relationship between tau pathology and cognition C) in EC or D) in the meta ROI. Stacked bar charts visualize proportion of total effect mediated by each factor.

EC cortical thickness ($P = 0.24$) mediated the relationship between EC tau and executive function performance (Fig. 3C), nor did the executive function network ($P = 0.41$) or meta ROI cortical thickness ($P = 0.09$) mediate the relationship between meta ROI tau and cognition (Fig. 3D). As an additional control, we found that episodic memory network strength did not mediate the relationship between meta ROI tau and executive function performance ($P = 0.14$), nor did executive function network strength mediate the relationship between meta ROI tau and episodic memory performance ($P = 0.48$; Fig. S3).

Network strength association with tau generalizes to an independent cohort

Finally, we assessed the extent to which these networks were associated with tau pathology in an independent cohort of older adults. We utilized rsfMRI and tau PET data from an ADNI3 sample of CU older individuals as well as patients with MCI (Table 1) to test the generalizability of the BACS-defined networks in their association with tau pathology burden. We computed rsFC between all 246 regions of the same whole-brain atlas (Fan et al. 2016) in ADNI participants, and network strength was derived by summing rsFC values of the BACS-defined episodic memory (Fig. 4A) and executive function (Fig. 4D) network connections in the independently collected and processed sample. We again used linear regression models adjusting for age, sex, mean framewise displacement, and the interval between rsfMRI and cognitive testing to examine the association between BACS-defined network strength and age as well as tau pathology in the ADNI sample. As in BACS, we observed a negative correlation between network strength and age for both episodic memory ($r = -0.30$, $P = 0.001$) and executive function ($r = -0.29$, $P = 0.001$; Fig. S2). Similar to the BACS sample, episodic memory network strength showed a moderate negative association with both EC tau ($\beta = -2.11$, $P = 0.083$; Fig. 4B) and a somewhat stronger association with meta ROI tau ($\beta = -2.65$, $P = 0.031$; Fig. 4C) adjusting for age, sex, mean framewise displacement, rsfMRI-PET interval, and rsfMRI-cognitive testing interval. In contrast with the BACS sample of only CU individuals, however, executive function network strength was also correlated with tau pathology in EC ($\beta = -2.06$, $P = 0.048$; Fig. 4E) and in the meta ROI ($\beta = -2.08$, $P = 0.048$; Fig. 4F).

To examine associations between BACS-defined network strength and cognition in the ADNI sample, we utilized previously computed memory and executive function cognitive domain scores (Gibbons et al. 2012) collected closest in time to each participant's fMRI scan ($M = 22.0$, $SD = 52.2$ d). Episodic memory network strength exhibited a bivariate correlation with memory performance ($r = 0.22$, $P = 0.012$), as did executive function network strength with executive function performance in ADNI ($r = 0.34$, $P < 0.001$). Adjusting for age, sex, mean framewise displacement, rsfMRI-cognitive testing interval, and years of education, the relationship between episodic memory network strength and memory performance in ADNI was attenuated ($\beta = 0.03$, $P = 0.31$), but executive function network strength remained significantly associated with executive function performance ($\beta = 0.08$, $P = 0.003$). Adjusting for these same factors, episodic memory network strength was weakly correlated with executive function performance ($\beta = 0.04$, $P = 0.07$), as was executive function network strength with memory performance ($\beta = 0.05$, $P = 0.07$; Fig. S4). Finally, we again examined the roles of network strength and cortical thickness in the tau-cognition relationship using multiple

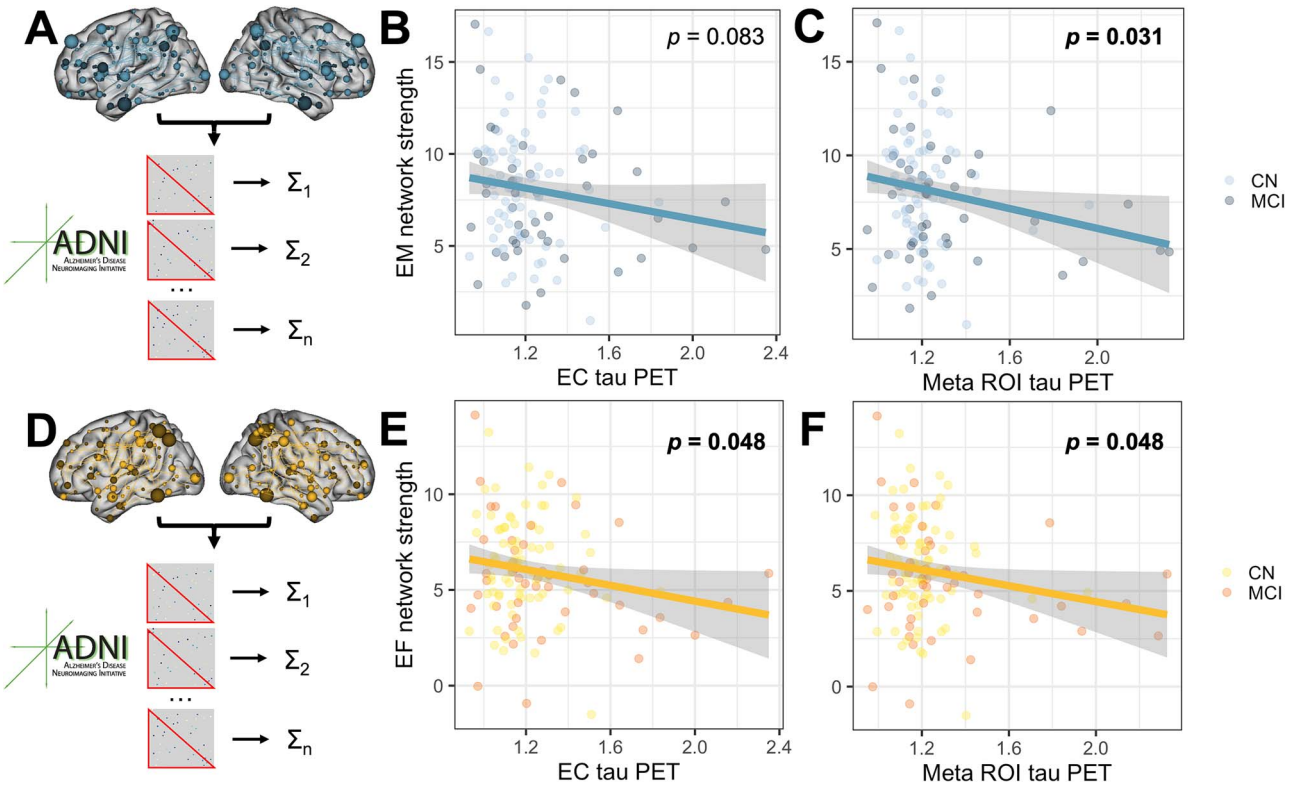

Fig. 4. Strength of BACS-defined networks is associated with tau pathology burden in ADNI participants. BACS-defined episodic memory A) and executive function networks D) were applied to ADNI participants and network strength was computed for each individual. B) Association between overall episodic memory network strength and EC tau PET. C) Association between episodic memory network strength and meta ROI tau PET. E) Association between executive function network strength and EC tau PET. F) Association between executive function network strength and meta ROI tau PET. Scatter plots are visualized effects of interest from linear regression models adjusted for age, sex, mean framewise displacement, rsfMRI-PET interval, and rsfMRI-cognitive testing interval.

mediation analyses in the ADNI sample. We found that episodic memory network strength did not significantly mediate the association between EC (7.2%, $P = 0.23$) or meta ROI (7.6%, $P = 0.22$) tau burden and episodic memory performance, while entorhinal cortical thickness (29.8%, $P = 0.01$) and meta ROI cortical thickness (28.0%, $P = 0.02$) did mediate this relationship (Fig. 5A and B). Executive function network strength exhibited a weak mediating role in the association between EC (14.0%, $P = 0.06$) and meta ROI (13.5%, $P = 0.07$) tau burden and executive function performance, as did entorhinal cortical thickness (18.0%, $P = 0.07$) and meta ROI cortical thickness (17.2%, $P = 0.13$; Fig. 5C and D). Taken together, our findings suggest that the strength of these functional networks in a separately collected and processed cohort of older adults exhibits similar relationships with age and tau pathology burden but does not demonstrate robust associations with cognitive performance per se.

Discussion

In this study, we used resting state fMRI in a cohort of CU older adults to identify functional networks related to both episodic memory and executive function performance. The episodic-memory-defined network was characterized by connections between the medial and lateral temporal cortex, the medial parietal and inferior parietal cortex, and the frontal regions, including the medial parietal prefrontal cortex. The parahippocampal gyrus, precuneus, and supramarginal gyrus tended to have the most connections with other brain areas in this network. Notably, the episodic memory network included connections between the hippocampus and anterior temporal as well as posterior medial regions. This pattern of connectivity is thought to be critical for memory processing and susceptible to age- and pathology-related alterations (Ranganath and Ritchey 2012). The executive function-defined network was characterized by connections between lateral temporal, superior parietal, and many superior frontal regions. Regions in the inferior parietal lobule and inferior temporal gyrus were particularly well-connected with the rest of the brain by this network. One striking anatomical feature of the executive function-defined network was connections with a cluster of regions in the dorsolateral prefrontal cortex (dlPFC). The dlPFC has long been implicated in the ability to manipulate information in the environment, such as rearranging of digits and making plans for the future (Gilbert and Burgess 2008). Directly comparing the anatomy of the 2 networks, the episodic memory network contained more regions, such as the parahippocampal gyrus, fusiform gyrus, and posterior cingulate cortex that are part of the limbic system and are affected early in the accumulation of tau pathology in aging and AD. Overall, the topography of these networks suggests that using cognitive performance to identify a sparse network of functional connections in the brain may provide insight into which connections throughout the brain are likely to be altered by the presence of tau pathology in aging and AD.

In the BACS sample of CU older adults, we found that greater tau pathology in both the EC and the temporal meta ROI was related to lower overall strength of the episodic memory-defined network but not the executive function-defined network. Episodic memory is often observed to be one of the first cognitive

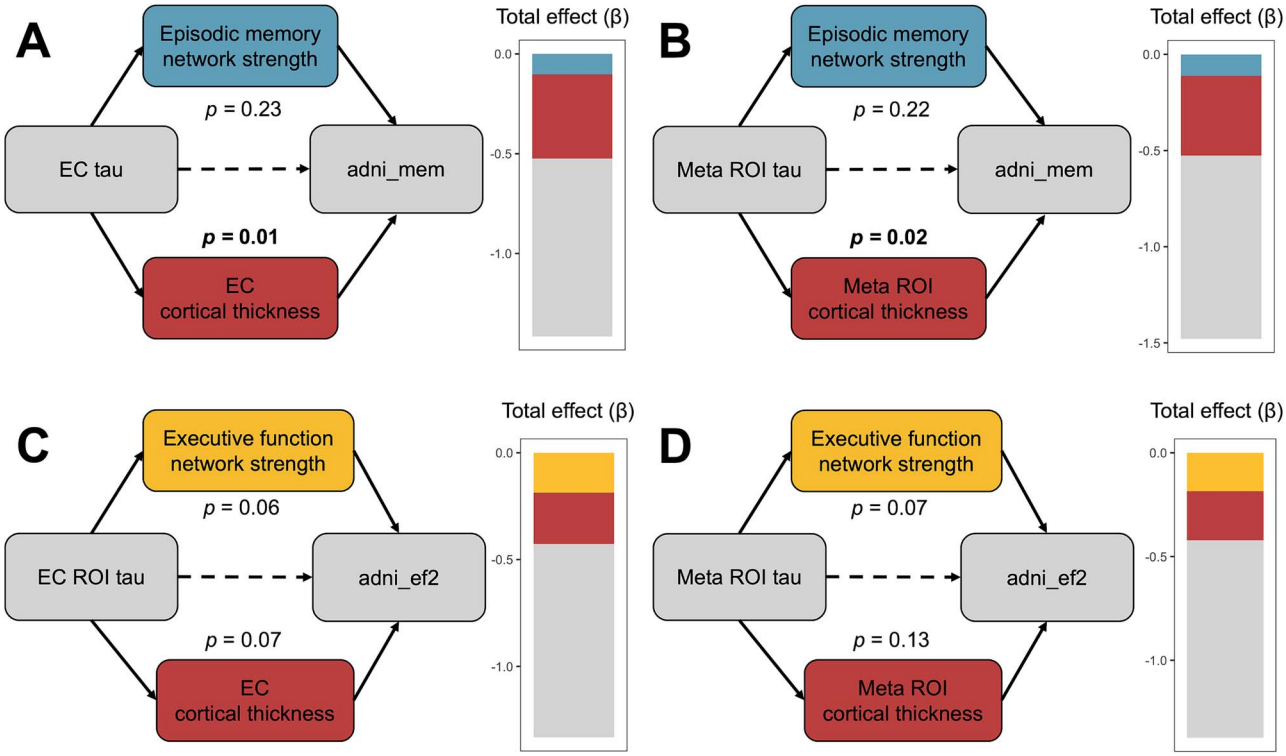

Fig. 5. Network strength does not robustly mediate the association between tau pathology and cognitive performance in an independent cohort. Multiple mediation models demonstrate that cortical thickness, but not episodic memory network strength, mediates the relationship between tau pathology and cognition, both A) in EC and B) in the meta ROI. Executive function network strength and cortical thickness show a weak mediating effect in the relationship between tau pathology and cognition C) in EC and D) in the meta ROI. Stacked bar charts visualize proportion of total effect mediated by each factor.

domains to decline in preclinical AD, and pathology-related disruption of connections specifically related to episodic memory plausibly underlies this deficit. Aberrant resting state FC between the hippocampus and other memory-related brain regions has previously been shown to differentiate CU older adults from those with impaired memory performance (Voets et al. 2014). Further, brain aging predicted from rsfMRI is accelerated in individuals with a history of familial AD and significant pathology burden (Gonneaud et al. 2021), and the discrepancy between chronological and brain age determined using rsfMRI has been shown to capture cognitive impairment (Liem et al. 2017). The networks identified in our study replicate these negative associations with age, but the relationship between episodic memory network strength and tau burden even after adjusting for participant age indicates that AD pathology may be driving functional impairment beyond the effects of normal aging. Indeed, the observed spatial distribution of tau pathology associated with reduced episodic memory network strength in our study resembles the typical pattern of AD-related tau deposition (Leuzy et al. 2021), revealing a phenotype typical of AD in CU older individuals.

Examination of the BACS-defined networks in the ADNI cohort provides replication and extension of our findings in BACS. We found associations between tau and reduced network strength for both episodic memory and executive function networks in ADNI participants, which may reflect more progressed disease given the inclusion of patients with MCI in the ADNI sample. Associations with the strength of both networks support the notion that both episodic memory and executive function domains tend to become impaired as individuals transition to MCI (Buckner 2004; Tideman et al. 2022). This was particularly the case for tau pathology in the temporal meta ROI, a group of regions where tau accumulation is thought to occur outside of the effects of normal aging (Jack et al. 2017). Though tau was correlated with the lower strength of both networks, the executive function network showed a stronger association with cognitive performance than did the episodic memory network after adjusting for factors such as age and sex. Though neither of these networks were observed to robustly mediate the effects of tau on cognition in the ADNI sample, measures of brain structure mediated this relationship more so than episodic memory network strength. Thus, the executive function network showed a somewhat more convincing association with cognition in the cohort of CU and MCI individuals, which may be related to the more advanced disease stage of the ADNI sample affecting cognitive domains other than episodic memory.

Another potential explanation for the limited replication of functional network mediation is differences in data acquisition between BACS and ADNI. Although fMRI data was processed as similarly as possible between the 2 samples, differences in scanners between sites and acquisition parameters make an exact comparison challenging. Further, although composite measures of episodic memory and executive function were used in both samples, the precise neuropsychological tests that were used to construct these measures differed between samples and may introduce additional variability. These differences are also informative, however, as they suggest that relationships between network strength and AD pathology can be replicated despite nonidentical data acquisition across samples. It should also be noted that replication of associations between cognitive and resting-state fMRI networks is challenging given the relatively high degree of variability inherent to this modality. Furthermore, the approach used here tends to identify networks with relatively

few functional connections compared to previous approaches (Rosenberg et al. 2015; Shen et al. 2017), favoring the interpretability of these networks in the context of aging and AD. However, it is possible that this sparsity may make it less likely to capture all of the many connections in the brain that are important for cognitive function, emphasizing the need for ongoing work to balance both the interpretability and generalizability of these behaviorally-meaningful functional networks.

The mediating roles of brain structure and function also hint at the differing biological consequences that this pathology can have in the aging brain. Though tau accumulation has been convincingly linked to neurodegeneration (La Joie et al. 2020), the role of structural measures in mediating its relationship with cognition has been inconsistently demonstrated (Bejanin et al. 2017; Berron et al. 2021), particularly for CU individuals (Ossenkoppele et al. 2021). Indeed, tau pathology has been shown to be more sensitive for detecting early cognitive change than either Aβ PET or structural measures (Ossenkoppele et al. 2019), and it has been proposed that functional changes such as network disruption may be a crucial mechanism for the effect of tau pathology on cognition (Jones et al. 2016; Ossenkoppele et al. 2021). Consistent with our results, tau pathology may eventually cause cognitive dysfunction through synaptic loss and neurodegeneration, but also more immediately via alterations in synaptic function (Harris et al. 2020). These distinct effects may help explain the limited role of neurodegeneration in cognitive impairment early in disease progression and suggest that the functional consequences of tau are more relevant for study and intervention at the earliest stages of decline (Ossenkoppele et al. 2021).

This study has several limitations. First, the BACS sample includes individuals with rsfMRI, tau PET, and cognitive testing collected within 1 yr of each other. Although alterations in brain tau and cognition are likely to occur very slowly in cognitively normal people, and we adjust for the time difference between the acquisition of these data in our analyses, our results may be impacted by these relatively liberal inclusion criteria. We also did not analyze the role of Aβ and chose to focus on tau pathology due to its closer relationship with cognition, but it is possible that there are interactions between tau and Aβ that we lack the statistical power to test. In addition, we took the approach of including only connections with a positive relationship to behavior in order to increase network sparsity and interpretability, but there may be functional connections negatively associated with behavior that are also important for cognition and influenced by the presence of pathology. We also did not precisely replicate associations between the BACS networks and cognition in ADNI, so further work is needed to identify generalizable networks with a more robust influence on cognition, perhaps defined using task fMRI. Finally, in order to make inferences about the role of these networks in cognitive decline, future work should examine longitudinal cognitive data rather than focusing exclusively on cross-sectional cognitive performance.

Taken together, our results suggest that behaviorally meaningful functional networks in fact play an important role in cognition in the early stages of AD. Despite skepticism over the relevance of resting state fMRI for predicting cognition (Finn 2021), the ubiquity and ease of collecting resting state data makes it a modality of great interest for potential clinical relevance (Adams et al. 2019; Franzmeier et al. 2020; Vogel et al. 2021). Overall, this study presents evidence that these networks are a compelling functional mechanism for the effect of tau pathology on cognitive performance in older adults. While neurodegeneration may account for more broad effects on cognition in the later stages of AD when tau pathology has been present for many years, reduced network integrity helps explain the impact of tau accumulation on cognitive function in older individuals without obvious structural atrophy.

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Author contributions

Jacob Ziontz (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Theresa M. Harrison (Conceptualization, Data curation, Methodology, Supervision, Writing—review & editing), Xi Chen (Methodology, Supervision, Writing—review & editing), Joseph Giorgio (Methodology, Writing—review & editing), Jenna N. Adams (Data curation, Methodology, Writing—review & editing), Zehao Wang (Visualization, Writing—review & editing), and William Jagust (Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing—review & editing).

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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